## Remarks

This Amendment Reply is in response to the Office Action dated April 20, 2007 and further to the personal interview dated June 27, 2007 with Examiner Kaufman. The Examiner is respectfully thanked for accommodating the interview request. During the interview attended by the inventor Dr. Ross Kedl, Chris Gram and the undersigned all of the outstanding rejections were discussed. Particularly, the 112 enablement, written description and second paragraph rejections were discussed. It is believed that the claims presented herein should render moot all the rejections as the present independent claims recited that the CD40 agonist or 4-1BB agonist directly binds the CD40 receptor or the 4-1BB receptor. In addition the recited TLR agonists are enabled and described by the as-filed specification.

In addition the anticipatory and obviousness rejections based on Krug et al and the Melief et al references were discussed in detail. It was argued by the inventor and representatives of Applicants that the primary reference Krug et al does not anticipate or render obvious the invention since the article does not teach or suggest a vaccine or immunostimulatory composition as claimed which is suitable for administration to a human subject in need thereof comprising the combination of a TLR agonist and a CD40 agonist or 4-1BB agonist as recited in the current pending claims. (See e.g., paragraph [029] which discloses that the subject immunostimulatory combinations are in a form wherein they "can be co-administered [e.g., in humans] to provide a therapeutic and/or prophylactic immunostimulatory effect".) By contrast, as noted in more detail below it was argued that the focus of the Krug reference instead was obtaining an alleged understanding of the mechanism by which a specific exogenously administered TLR agonist compound, CpG, elicits a profound effect on immunity in vivo based on in vitro studies which allegedly established that exogenous CpG acts in concert with endogenous T cells which express CD40L. It was noted that the reference "shows this" by co-

culturing a specific set of dendritic cells, plasmacytoid cells, with CpG, Il-3 and CD40L transfected cells, and which are further contacted with allogeneic allegedly naïve T cells.

Applicants noted that a skilled artisan would not have reasonably extrapolated based on the reported observations of Krug et al. that similar effects would be observed in vivo or that CpG and CD40L should or could be co-administered to a human subject as claimed.

In support thereof it was noted that the compositions used by Krug et al. in their in vitro studies contain CpG, IL-3, CD40L transfected BHK cells and allogeneic naïve T cells and would not be suitable for use in immunotherapy or immunoprophylaxis of human subjects. Particularly it was explained that the Krug compositions comprise in vitro cell cultures designed to study CpG in vitro that comprise a specific subpopulation of dendritic cells (plasmacytoid cells) which are cultured with IL-3 and other constituents and further are incubated with CpG and/or foreign (hamster) cells that express CD40L on their surface. It would be absolutely clear to one of skill in the art that such compositions containing foreign cells and allogeneic dendritic cells would not be suitable for human immunotherapy and would moreover not be anticipated to elicit a synergistic effect with respect to the immune response generated against an antigen in a human subject as required by the present claims. To the contrary, it would be expected that the CD40L expressing BHK cells, because of their being foreign (non-human), would be immunogenic and therefore likely be rapidly cleared from the circulation and therefore not elicit a synergistic effect on antigen specific immunity in a human subject.

Also, it was argued that the reference would not render the subject synergistic immunostimulatory compositions or vaccines anticipated or obvious since the results which were observed in vitro using cultured plasmacytoid cells, IL-3, CpG, and CD40L-transfected BHK cells could not reasonably be extrapolated to the in vivo effects of a composition suitable for human immunotherapy as claimed containing a TLR agonist and CD40L. For example it was noted that at the time of invention and up to the present date the effects of plasmacytoid cells on adaptive antigen specific immunity (which comprise only a small subset of human dendritic cells) have not been widely accepted by those skilled in the art. Reference was made to several

publications which are cited herein. Therefore, what Krug allegedly observed in vitro would not have been viewed by a skilled artisan to teach or suggest the subject immunostimulatory or vaccine compositions suitable for human immunotherapy or to be predictive as to the effect of the subject immunostimulatory combinations in vivo, i.e. synergistic effect on an antigen specific immune response in a human subject.

Also it was noted by the inventor that the in vivo mechanism by which TLR/CD40 agonist combinations elicits synergy in vivo (CD70 upregulation on certain dendritic cells) is not attributable to plasmacytoid dendritic cells as evidenced by experiments conducted by the present inventors which revealed that these cells do not express CD70 when contacted with CD40L or an agonistic CD40 antibody and a TLR agonist in vivo. (A publication by an inventor, Ross Kedl, containing these experiments is provided). Further based thereon, it was argued that while the Krug reference allegedly suggests that their results obtained in vitro with plasmacytoid cells allegedly suggest what happens in vivo upon CpG administration, that this is not the case, and that in fact later in vivo data suggests that plasmacytoid cells seem to play no causal effect in the synergistic effects of CD40/TLR agonist combinations on adaptive immunity..

It was also explained at the interview that the Krug mixed cell compositions would not be suitable for human immunotherapy (such as administered orally or by injection) and further that the Krug reference at no point suggests co-administering or producing an immunostimulatory composition suitable for human immunotherapy as claimed herein comprising CD40L and a TLR agonist which are comprised in synergistically effective amounts as claimed herein. In further support thereof it was noted that a prominent author included on the Krug reference, Arthur Krieg, while having a large number of publications and issued patents and pending patent applications relating to CpG, and its use as an immune agonist, does not disclose or claim such a synergistic immunostimulatory composition in any published patent application known to Applicants. It was argued that this provides further evidence as to the non-obviousness of the claimed invention to those skilled in the relevant art.

Related to the foregoing, it was further noted by the inventor that the present inventors are widely recognized as being the innovators of the discovery that CD40 agonists and TLR agonists elicit a synergistic effect on immunity and that supporting citations would be provided with the next response. A listing of these citations are provided herein. .

Still further it was noted by the inventor that at the time of the present invention the co-administration of a TLR agonist and a CD40 agonist to a human subject (absent the benefit of Applicant's invention and data) would not have been obvious since CD40 agonists such as CD40L when administered as a monotherapy were then known to elicit toxic side effects in vivo and it reasonably would have been anticipated that a TLR agonist likely would have exacerbated these toxic side effects By contrast, the present inventors discovered that not only does the subject immunostimulatory combination synergistically enhance antigen specific immune responses, that such compositions also elicit no appreciable toxicity in vivo at these synergistic dosages. This result was totally unanticipated by the prior art. (Supporting publications and data are cited and provided herein.)

Finally at the interview it was noted that method claims would be submitted in the next response which are directed to use of the subject immunostimulatory or vaccine compositions for human therapy and that these claims would exactly parallel the scope of the present claims (which are believed to be in condition for allowance as they are enabled and adequately described and further are not anticipated or rendered obvious by Krug et al alone or in combination with Melief et al). These method claims correspond to new claim 91-107 presented in this Amendment.

Turning now to the claim amendments introduced herein, Applicants note that in order to avoid any printer errors and to facilitate grant that all the prior claims 1-57 are cancelled without prejudice to the subject matter contained therein in favor of new claims 58-107. The composition claims find support in the original claims and in the specification and are drafted consistent with the proposals set forth at the recent interview. For example, the claims specify that the CD40 agonist or the 4-1BB agonist directly binds the CD40 receptor or the 4-1BB

receptor. Also the independent composition claims specify that the immunostimulatory composition is suitable for human immunotherapy and that the composition elicits a synergistic effect on the immune response to an antigen in a human subject in vivo. As noted above, specific support for the amendatory language may be found e.g., in paragraphs [029] aforementioned and paragraphs [072-074] of the specification which disclose that the immunostimulatory combinations are useful in human therapy or prophylaxis and recite different modes of administration (as recited in several of the new claims) and paragraphs [062-063] of the as-filed specification which disclose synergistic dosages which may vary dependent on various factors including the host species to which it is administered. In addition, it is noted that all the newly submitted therapeutic method claims depend from the composition claims so that the scope thereof is parallel therewith in accord with the Examiner's admonition. Based on the foregoing reconsideration and withdrawal of the rejections are respectfully requested.

**Claim Amendments**

As noted Claims 1-57 have been canceled without prejudice in favor of new claims 58-107 . Applicants reserve the right to pursue one or more of the canceled claims in one or more continuation or divisional applications.

The new claims parallel and find support in the prior claims except that the independent claims now recited that the CD40 agonist or the 4-1BB agonist directly binds CD40 or 4-1BB. Support for this change may be found at paragraph 26 of the specification. In addition the claims now specify that the immunostimulatory composition is suitable for human immunotherapy and elicits a synergistic effect on an antigen specific immune response therein. Specific support is found in paragraphs 72-75 and 62-63 et al. which disclose that the subject compositions are potentially for human immunotherapy and that the dosages of the agonists will be selected so as to achieve a synergistic effect on antigen specific immunity in the species (human) of usage. The method claims correspond to the composition claims except that they provide for these compositions to be administered to a human subject in need thereof wherein they elicit a

synergistic effect on immunity. These claims find support at least in the same paragraphs of the as-filed specification as well a the original method of use claims.

. No new matter is introduced by these amendments.

**The 35 U.S.C. §112, First Paragraph, Rejections**

Claims 1-5, 8-10, 49-53, and 55-57 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was allegedly not sufficiently described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Office Action states that while agonists that directly bind to activate a receptor are described to meet the requirements of 35 U.S.C. § 112, first paragraph, agonists that indirectly activate a receptor are not described to satisfy the requirements of 35 U.S.C. § 112, first paragraph.

Applicants have drafted the newly submitted independent claims 58 and 73 to recite that the immunostimulatory composition or vaccine includes a CD40 agonist or a 4-1BB agonist, that directly binds CD40 or 4-1BB, thereby rendering the rejection moot. In addition and as discussed at the recent interview, Applicants note that other CD40 direct binding agonists are known in the art such as a heat shock protein Hsp70 (Wang et al., Immunity, 15:971-983 (2001); Pido-Lopez et a., J Immunol. 178:1671-1679(2007)); trimeric CD40L (Fournel et al., Nature Chemical Biology 1(7):377-382(2005)); and CD40L mimetics (Habib et al., J Immunol. 178:6700-6704 (2007)). These references are provided herewith.

Each of the remaining pending claims depends, directly or indirectly, from the independent claims and therefore, contains all of the features recited therein. Therefore, Applicants submit that each of claims 58-107 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, for at least the reasons that claims 58 and 73 satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

Applicants respectfully request that the prior rejection of claims 1-5, 8-10, 49-53, and 55-57 as failing to satisfy the written description requirement of 35 U.S.C. §112, first paragraph, not be maintained against the new claims.

Claims 1-5, 8-10, 49-53, and 55-57 stand rejected under 35 U.S.C. §112, first paragraph, as failing to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. Specifically, while the Office Action acknowledges that Applicants' disclosure is enabling for a CD40 agonist that directly binds to CD40 and for a 4-1 BB agonist that directly binds to 4-1BB, it asserts that Applicants' disclosure does not reasonably provide enablement for indirect CD40 or 4-1BB agonists. The Office Action further asserts that Applicants' disclosure fails to reasonably enable one skilled in the art to make and use the invention with respect to agonists of TLR10.

Claims 1 and 49 have been amended to recite that the immunostimulatory composition (in the case of claim 58) or vaccine (in the case of claim 73) includes a CD40 agonist or a 4-1BB agonist that respectively directly bind CD40 or 4-1BB , thereby rendering the rejection moot.

Claims 58 and 73 also have been drafted and the dependent claims to render the issue with respect to TLR10 agonists moot. Therefore, Applicants submit that claims 58-107 satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, for at least the reasons that claims 58 and 73 satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

Applicants respectfully request that the rejection of claims 1-5, 8-10, 49-53, and 55-57 as failing to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, be withdrawn and not applied against new claims 58-107.

**The 35 U.S.C. §112, Second Paragraph, Rejection**

Claims 1-5, 8-10, 49-53, and 55-57 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Office Action asserts that the

definition of the term "agonist" in Applicants' disclosure is so broad that the metes and bounds of the invention are unclear.

This rejection was discussed at the recent interview. Consistent therewith new independent Claims 58 and 73 have been drafted to recite that the immunostimulatory composition (in the case of claim 58) or vaccine (in the case of claim 73) includes a CD40 agonist or a 4-1BB agonist, that directly binds CD40 or 4-1BB thereby rendering the rejection moot.

Each of claims 59-72 and 74-107 depends, directly or indirectly, from claim 58 or 73 and therefore, contains all of the features recited in these independent claims. Therefore, Applicants submit that claims 58-107 satisfy the requirements of 35 U.S.C. § 112, second paragraph, for at least the reasons that claims 58 and 73 satisfy the requirements of 35 U.S.C. § 112, second paragraph.

Applicants respectfully request that the rejection of claims 1-5, 8-10, 49-53, and 55-57 under 35 U.S.C. §112, second paragraph, be withdrawn and not applied against new claims 58-107.

**The 35 U.S.C. §102 Rejection**

Claims 1-4 and 9 stand rejected under 35 U.S.C. §102(b) as being anticipated by Krug et al. ("Toll-like receptor expression reveals CpG DNA as a unique microbial stimulus for plasmacytoid dendritic cells which synergizes with CD40 ligand to induce high amounts of IL-12," *Eur. J. Immunol., 31*:3026-3037; Oct. 2001).

M.P.E.P. § 2131 states, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (quoting *Verdegaal Bros. V. Union Oil Co. of California*, 814 F. 2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants submit that Krug et al. cannot anticipate Applicants' claims because Krug et al. fails to set forth, either expressly or inherently, each and every element of Applicants' claims.

As discussed above, the only pending independent claims 58 and 73 and all of the claims dependent thereon are directed to immunostimulatory or vaccine compositions suitable for human immunotherapy (or methods of use) that when administered to a human subject in need of immunotherapy elicit a synergistic effect on the immune response to an antigen. As further noted above the as-filed specification makes explicitly and implicitly clear e.g., in paragraphs [029], [072-075] and [062-063] of the as-filed specifications that the inventive immunostimulatory combinations and vaccine compositions containing expressly include those which are formulated in a manner that is suitable for human immunotherapy and that such compositions, based on factors including the specific dosages of the CD40 agonist, TLR agonist and antigen (where present) will elicit a synergistic effect in the immune response to an antigen in the host of administration (herein a human subject). The specification therein further discloses various modes of administration including oral, injection (various types of injection routes) and teaches that pharmaceutically acceptable excipients and carriers may be present and identifies potential dosage forms such as tablets and injectables. Also, in paragraphs [062-063] the application teaches that the dosages and ratios may vary and will depend on factors including the species of administration (herein human).

Therefore, it is clear from the as-filed specification that the invention encompasses immunostimulatory and vaccine compositions as claimed comprising a TLR agonist and a CD40 or 4-1BB agonist wherein the composition is suitable for use in human immunotherapy wherein it will yield a synergistic enhancement in immunity to an antigen. By contrast, the Kug et al. (Id.) reference does not anticipate or envision an immunostimulatory or vaccine composition suitable for human immunotherapy and containing dosages of a TLR agonist and a CD40 or 4-1B agonist that elicit a synergistic effect on antigen immunity in a human subject as presently claimed. By contrast, Krug et al merely teaches in vitro cultures containing a specific population of dendritic cells (plasmacytoid cells) that are cultured with IL-3, CpG and/or CD40L transfected baby hamster kidney cells (BHK cells) which thereafter are further contacted with allogeneic naïve T cells. This is clear upon reading the Krug reference in its entirety and especially the Materials and Methods

section of the reference at pages 3303-3034 (see especially 4.3 and 4.6 which disclose the co-culture of plasmacytoid dendritic cells incubated with Il-3, CD40L transfected BHK cells and CpG oligonucleotides and Figure 5 at page 3031 which clearly describes in the legend that the in vitro effects on plasmacytoid cells and the production of various cytokines thereby was allegedly tested in vitro by contacting cultures of plasmacytoid cells with various stimuli including a combination of CpG and CD40L transfected cells. (The fact that CD40L transfected cells were used is further clear from the fact that their experiments include the use of a control which comprises a cell line that was not transfected with CD40L). Thus, the Krug reference in its four corners does not teach a composition suitable for human immunotherapy containing at least one CD40 agonist and at least one TLR agonist. It would be apparent that BHK cells would not be suitable for use in human immunotherapy administered by any means. For example, it would be apparent that the compositions of Krug if injected would be immunogenic and also suffer from safety issues based on the presence of foreign (hamster) cells. Also, the Krug compositions based on their nature would not be suitable for oral administration since the CD40L expressing cells would most likely not be stable in the gut. Similarly, the Krug composition would not be suited for transmucosal delivery to a human (or any subject) since it is not in a form that would facilitate transdermal delivery of the CpG and CD40L agonist compounds.

Rather, and as explained by the inventor at the recent interview it would be readily apparent to a skilled artisan in possession of the Krug reference and an understanding of the compositions reported therein comprising a mixture allogeneic plasmacytoid dendritic cells (contacted with IL-3) and further comprising CpG and CD40L-transfected non-human ( baby hamster kidney cells) that these compositions would not be suitable for use as a human immunotherapeutic or as a human vaccine. For example the hamster cells would be expected to be immunogenic in humans and therefore not be a suitable source of exogenously administered CD40L. In addition it would be anticipated that the cell cultures of Krug containing these foreign cells would not elicit any synergistic effect on antigen specific immunity in a human subject. Rather the more reasonable

expectation would be that the foreign BHK cells would be rapidly cleared and consequently not elicit any synergistic effect on immunity. Therefore, at the least this reference should not anticipate the claimed immunostimulatory compositions or methods of use thereof as vaccines and as immunostimulatory combinations.

Therefore, withdrawal of the 102 anticipation rejection based on Krug is respectfully requested. Particularly, at least based on the foregoing, Applicants respectfully request that the rejection of prior claims 1-4 and 9 under 35 U.S.C. §102(b) not be maintained against any of the current claims..

**The 35 U.S.C. §103 Rejection**

The Examiner rejected claims 10, 49, 51, 56, and 57 under 35 U.S.C. §103(a) as being unpatentable over Krug et al., as applied to claims 1-4 and 9, in view of Melief et al. ("Effective therapeutic anticancer vaccines based on precision guiding of cytolytic T lymphocytes," *Immunol. Rev.*, *188*:177-182; Oct. 2002).

§ 706.02(j) of the M.P.E.P. states that to establish a *prima facie* case of obviousness, three basic criteria must be met:

(1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference(s) or combine the reference teachings;

(2) there must be a reasonable expectation of success; and

(3) the prior art references, when combined, must teach or suggest all of the claim limitations.

Applicants respectfully submit that the Krug et al reference taken alone or in view of Melief et al. does not teach or suggest the subject immunostimulatory compositions or vaccines as claimed which are suitable for human immunotherapy and which contain dosages of a TLR agonist and a CD40 agonist which elicit a synergistic effect on antigen specific immunity in a human subject. For the same reasons set forth in the traversal of the 102 rejection Krug et al does

not teach any composition within its "four corners" suitable for use in human immunotherapy in eliciting a synergistic adjuvant effect. Rather, the focus of the Krug reference is in vitro studies the purported aim of which is to obtain a better understanding of how CpG works in vivo in humans and in particular what immune cells and TLR moieties that CpG interacts. This is clear for example from the abstract wherein the authors state that their studies show that CpG stimulated PDCs "is under the strict control of two signals, an adequate exogenous microbial stimulus such as CpG ODN, and CD40L provided endogenously by activated T cells." This is further clear from their statements in the paragraph bridging pages 3026-3027 wherein the authors note that "the effects of CpG DNA on the murine immune system are well characterized". and that "recent progress has been made regarding the understanding of CpG mediated effects o in the human immune system". Also, that this is the focus of the reference is clear from their statement that the "present study we found that TLR9 expression is associated with selective recognition of CpG ODN by PDC but not by MDC. ".

Therefore, it is clear from the Krug reference that their in vitro studies are focused on understanding why CpG DNA as an vaccine adjuvant "is at least as effective as the gold standard complete Freund's adjuvant (CFA) but has higher Th1 activity and lower toxicity". The fact that Krug et al did not envision or suggest the subject immunostimulatory combinations is further clear from the fact that at no place in the reference do they teach or suggest compositions suitable for in vivo co-administration of CpG and CD40L as claimed. Rather in Krug the CD40L is meant to mimic the effects of endogenous CD40L expressed on the surface of activated T cells and potentially explain why CpG is such a powerful adjuvant.

The fact that Krug would not suggest to a skilled artisan a composition suitable for human immunotherapy comprising the combination of CD40 agonist and a TLR agonist is further evidenced by the fact that the authors of the Krug reference which include Arthur Krieg, a prominent researcher in the design and use of CpG DNAs as immune adjvants with over 90 published patent applications and issued patents does not disclose in any of these patent applications compositions comprising the combination of a CD40 agonist and a TLR agonist as

claimed. Applicants have reviewed the published patent specifications for all patent applications and patents that identify Arthur Krieg as an inventor relating to CpG (list of patents and published patent applications listing Arthur Krieg and/or Krug as an inventor and mentioning CpG is provided as Appendix A to this Amendment). Based on Applicants' review thereof they could not identify not a single instance wherein such combinations were envisioned by the patentees or applicants. This is respectfully believed to provide further evidence that the studies reported by Krug et al (which included Arthur Krieg) would not have suggested to a skilled artisan such as Dr. Krieg that CpG and CD40L should be co-administered. Rather, as argued., the only reasonable inference that potentially can be drawn from Krug et al. is that CpG may enhance immunity based on its effect on certain immune cells and that this ay involve endogenous activated T cells which express CD40L.

Additional evidence that support such a conclusion is the fact that the present inventors are widely recognized by their peers as being the innovators of CD40L/TLR agonist combinations and the synergistic effects thereof on adaptive antigen specific immunity in vivo. As noted at the recent interview the first publication as to the synergistic effects of TLR/CD40 agonist combos in vivo on adaptive immunity is a publication by the present inventors , Ahonen et al., J Exp Med. 199(6):775-784 (March 15, 2004). This publication is widely cited by scientific peers of the inventors as to being the first evidence as to the synergistic effects of TLR/CD40 agonists in vivo. As evidence of this fact a listing of references citing the Ahonen article is attached to this Amendment Reply as Appendix B.

Yet another reason why one skilled in the art would nor have reasonably extrapolated from the teachings of Krug et al the invention as set forth in the present claims (which are all directed to immunostimulatory compositions for use in human immunotherapy or use thereof comprising the synergistic combination of at least one CD40 or 4-1BB agonist and at least one TLR agonist) is the fact that the Krug reference only contains in vitro studies and moreover uses therein a type of dendritic cell (plasmacytoid dendritic cell) which is and was not at the time of this invention thought to play a demonstrable role in adaptive antigen specific immunity.. In

support thereof and as discussed at the recent interview Applicants refer to two publications by Forteneau et al., i.e. Forteneau et al., J. Virol. 78(1): 523-32 (2004) and Forteneau et al., Blood 101(9):3520-6 (2003). Both of these publications suggest that conventional myeloid dendritic cells instead play a much more significant effect than plasmacytoid cells do on adaptive antigen specific T cell immunity.

In addition, in vivo studies by the inventors have shown that plasmacytoid cells do not appear to play a role in the manner by which CD40 agonists and TLR agonists in combination elicit a synergistic effect on antigen specific T cell immunity. This article (Sanchez et al., J Immunol. 178:1564-1572 (2007)) which includes Ross Kedl as the last author contains in vivo data demonstrating that the synergy elicited by TLR/CD40 agonist combinations is attributable to the upregulation of CD70 on certain dendritic cells in vivo. As reported therein, the dendritic cells which overexpress CD70 do not include plasmacytoid dendritic cells. Therefore, the biological mechanism which explains why TLR/CD40 agonists elicit a synergistic effect on adaptive T cell immunity in vivo does not appear to involve the plasmacytoid cell which were studied in vitro by Krug et al.

Still further, and as further explained at the interview the Krug reference and the state of the art would not have reasonably suggested the co-administration of a TLR agonist such as CpG with a CD40 agonist such as a CD40 agonistic antibody or a CD40L polypeptide. To the contrary, this would have been disfavored since the toxic effects of CD40L monotherapies in both rodents and humans were then known (liver toxicity). Therefore the combination as an immunotherapeutic for use in humans would have been disfavored given the reasonable expectation that the combination of 2 proinflamatory molecules, i.e., CD40L and CpG, would resulted in even greater toxicity. Quite surprisingly the present inventors have discovered that the reverse is true, i.e., that co-administration of CD40L and a TLR agonist results in reduced toxicity, and a synergistic enhancement in antigen specific immunity. (See Appendix C containing in vitro toxicity data obtained by the inventors relating to TLR/CD40 agonist combinations).

Therefore, the present invention achieves unexpected results in 2 aspects, i.e., an unexpected synergistic enhancement in in vivo immunity and a reduction in in vivo liver toxicity (not observed at synergistic dosages) therefore making the subject immunostimulatory combination well suited for use as an improved immune adjuvant in humans.

Based on the foregoing Krug et al taken alone does not teach or suggest the present immunostimulatory composition or its inherent advantages. In addition, the invention is further not suggested by Krug et al in view of Melief et al. To the contrary, as acknowledged in the prior Office Action this reference similarly does not teach or suggest the synergistic immunostimulatory or vaccine compositions claimed herein comprising synergistic dosages of a CD40 or 4-1BB agonist and a TLR agonist that are suitable for use in human immunotherapy.

For the same reasons, the dependent claims are not suggested by Krug et al alone or in combination with Melief et al. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) based on Krug et al in view of Melief et al be withdrawn and not applied against any of the current pending claims 58-107.

## Summary

For the reasons articulated herein and at the recent personal interview, it is respectfully submitted that the pending claims 58-107 are in condition for allowance and notification to that effect is respectfully requested. As further discussed at the recent interview if any issues remain outstanding upon consideration of this Reply The Examiner is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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